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Basis for recognition of cisplatin-modified DNA by high-mobili group proteins.

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The anticancer activity of cis-diamminedichloroplatinum(II) (cisplatin) arise ability to damage DNA, with the major adducts formed being intrastrand d((d(ApG) crosslinks. These crosslinks bend and unwind the duplex, and the al structure attracts high-mobility-group domain (HMG) and other proteins. Tl of HMG-domain proteins to cisplatin-modified DNA has been postulated to the antitumour properties of the drug. Many HMG-domain proteins recogni DNA structures such as four-way junctions and cisplatin-modified DNA, bu now the molecular basis for this recognition was unknown. Here we describ mutagenesis, hydroxyl-radical footprinting and X-ray studies that elucidate t structure of a 1:1 cisplatin-modified DNA/HMG-domain complex. Domain . structure-specific HMG-domain protein HMG1 binds to the widened minor a 16-base-pair DNA duplex containing a site-specific cis-[Pt(NH3)2[d(GpG N7(2)]] adduct. The DNA is strongly kinked at a hydrophobic notch create platinum-DNA crosslink and protein binding extends exclusively to the 3' si platinated strand. A phenylalanine residue at position 37 intercalates into a hydrophobic notch created at the platinum crosslinked d(GpG) site and bind domain is dramatically reduced in a mutant in which alanine is substituted fo phenylalanine at this position.

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